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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,149	10/19/2001	R. Preston Mason	2189 P01 US CIP	2552

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EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 11/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,149	MASON, R. PRESTON	
	Examiner	Art Unit	
	Shaojia A. Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 29-65* is/are pending in the application.

4a) Of the above claim(s) *29-56 and 60-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,57-59 and 63-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 19, 2004 has been entered.

This Office Action is a response to Applicant's request for continued examination (RCE) filed July 19, 2004, and amendment and response to the Final Office Action (mailed January 29, 2004), filed July 19, 2004 wherein claims 7-14 and 22-28 are cancelled, and claims 1-6, 57-59, and 63-65 have been amended; claims 66-68 are newly submitted.

Currently, claims 1-6, 29-56, 57-59, and 60-65 are pending in this application.

It is noted that claims 29-56 and 60-62 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, of record in the previous Office Action dated January 29, 2004.

Claims 1-6 and 57-59 as amended now, and new claims 63-68 are examined on the merits herein.

Applicant's declarations of Dr. R. Preston Mason (inventor), and Dr. J. Wouter Jukema (not inventor) under 37 CFR 1.132 submitted July 19, 2004 and May 3, 2004, are acknowledged and will be further discussed below.

Applicant's declarations of Dr. R. Preston Mason (inventor) under 37 CFR 1.132 filed July 19, 2004 and May 3, 2004, presenting the unexpected and/or synergistic antioxidant effects of the combination of amlodipine and atorvastatin, obtained from the experimental tests in vitro, e.g., with p value < 0.0001, (see particularly Figure 1 (A and B) and Figure 2 of the declaration May 3, 2004 and the description and explanation of the experimental evidence at page 3-5 of the declaration July 19, 2004) have been considered and are sufficient to overcome the prior art rejection made under 35 U.S.C. 103(a) as being unpatentable over Davidson et al. (4,879,303) and Bjorge et al. (5,385,929) in view of Jekema et al. (Arteriosclerosis, Thrombosis, and Vascular Biology, Vol. 16, No.3, 1996, p425-430), and Merck Index of record in the previous Office Actions dated January 29, 2004.

Therefore, the said rejection is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 68 is rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling the combination of amlodipine and atorvastatin metabolite further comprising the particular and

specific antioxidant, does not reasonably provide enablement for any substances or compounds represented by "an endogenous and/or exogenous antioxidant".

The recitation, "an endogenous and/or exogenous antioxidant" is seen to be merely functional language.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to the combination of amlodipine and atorvastatin metabolite further comprising "an endogenous and/or exogenous antioxidant".

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims are deemed very broad since the claim may reasonably encompass not only those known but also unknown "an

endogenous and/or exogenous antioxidant" as of the instant filing date, even those future known ""an endogenous and/or exogenous antioxidant".

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate". The CAFC further clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphases added).

In the instant case, "an endogenous and/or exogenous antioxidant", recited in the instant claim is purely functional distinction. Hence, the functional recitation read on any known or unknown or future known compounds that might have the recited function. However, the specification merely provides the particular and specific antioxidants for the composition in the claim (see page 12 of the specification).

Thus, Applicants functional language at the points of novelty fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicants', neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited of monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)).

The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects, side effects, and especially serious

toxicity that may be generated by drug-drug interactions when and/or after administering to a human the ***combination*** of amlodipine and atorvastatin metabolite and any substance or compound represented by "an endogenous and/or exogenous antioxidant".

See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed, 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added). In the instant case, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having claimed functional properties in the pharmaceutical compositions herein to be administered to a host. Thus, the teachings of the book clearly support that the instant claimed invention is highly unpredictable.

Further, these recitations may broadly encompass those known and **unknown** antioxidants as of the instant filing date, as discussed above. Note those **future known** antioxidants yet to be discovered and/or made. Hence,

those unknown or future known antioxidants encompassed by claim 68 herein must require to additional or future research to discover, establish or verify their usefulness. Therefore, as indicated in the previous Office Action, the skilled artisan has to exercise **undue experimentation** to practice the instant invention. The presence or absence of working examples and the quantity of experimentation necessary:

The specification fails to provide clear and convincing evidence in sufficient support of the administration to a human or *vitro* testing the ***combination*** of amlodipine and atorvastatin metabolite and any substance or compound represented by "an endogenous and/or exogenous antioxidant". As a result, necessitating one of skill to perform an exhaustive search for the embodiments of any known and unknown antioxidants encompassed in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the cases *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the

instant claims and their combinations employed in the claimed compositions to be administered to a human, with no assurance of success.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-3 and 58-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation, "derivative of amlodipine" render claims 2-3 and 58-59 indefinite. The recitation, "derivative of amlodipine " is not clearly defined in the specification. Hence, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to " derivative of amlodipine ", since one of ordinary skill in the art would clearly recognize that that " derivative of amlodipine " read on many widely varying groups possibly substituting amlodipine. Given the fact that any significant structural variation to a compound would be reasonably expected to alter its properties, e.g., physical, chemical, physiological effects and functions.

Thus, it is unclear as to "derivative of amlodipine" herein encompassed thereby.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 57-59 and 63-67 are rejected under 35 U.S.C. 102(b) as being anticipated by the Pfizer News, May 20, 1997 (PTO-892).

The Pfizer News discloses the combination of Norvasc also known as amlodipine besylate (See FDA approval February 7, 1995, PTO-892) and Lipitor also known as atorvastatin calcium in their effective amounts for treating cardiovascular diseases (see the 4th paragraph of page 2 of Pfizer News). Hydroxylated atorvastatin metabolite claimed herein is a metabolite of atorvastatin, which was necessarily produced in the patient's body upon ingestion of atorvastatin. Note that the court ruled that the metabolite of loratadine called descarboethoxyloratadine or "DCL" was INHERENTLY anticipated by loratadine (Claritin ™) because it was necessarily produced in the patient's body upon ingestion of Claritin ™. See Schering Corp. v. Geneva Pharmaceuticals, Inc., 68 USPQ2d 1760 (CAFC 2003). Thus, atorvastatin disclosed by the Pfizer News would anticipate hydroxylated atorvastatin metabolite. Moreover, the tablets of Norvasc and Lipitor are known to comprise pharmaceutical acceptable carriers or diluents.

Further, note that it is well settled that "intended use" of a composition or product, e.g., the recitation, "inhibit lipid peroxidation in human LDL or lipid membrane to achieve a therapeutic effect", will not further limit claims drawn to a composition or product, so long as the prior art discloses the same composition comprising the same ingredients in an effective amount as the instantly claimed. See, e.g., *Ex parte Masham*, 2 USPQ2d 1647 (1987) and *In re Hack* 114, USPQ 161. Note that the combination of the prior art cited herein would certainly inhibit lipid peroxidation in human LDL or lipid membrane to achieve a therapeutic effect

Thus, the combination of the prior art cited herein anticipates the instant claimed composition.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over the Pfizer News, May 20, 1997 in view of Gilligan et al. (Journal of the American College of Cardiology, (1994 Dec) 24 (7) 1611-7, PTO-892).

The same disclosure of the Pfizer News has been discussed in the 102(b) rejection set forth above.

The News does not expressly disclose the combination therein further comprising an antioxidant.

Gilligan et al. teaches that antioxidants such as Vitamin A, C, and E, are known to be used in the treatment of hypercholesterolemia in humans. See the abstract and entire article.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to further employ antioxidants such as Vitamin A, C, and E in the composition for treating hypercholesterolemia or atherosclerosis.

One having ordinary skill in the art at the time the invention was made would have been motivated to further employ antioxidants such as Vitamin A, C, and E in the composition for treating hypercholesterolemia or atherosclerosis since the combination of amlodipine and atorvastatin, and antioxidants such as Vitamin A, C, and E are known to be used in the treatment of hypercholesterolemia in humans according to the prior art cited herein.

Therefore, one of ordinary skill in the art would have reasonably expected that adding an antioxidant such as Vitamin A, C, and E to the combination of amlodipine and atorvastatin would improve the anti-lipidemia effect of the combination.

Since all active composition components herein are known, it is considered prima facie obvious to combine them into a single composition useful for the very same purpose. At least additive therapeutic effects would have been reasonably expected. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 57-59 and 63-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 118-147 of copending Application No. 10/214,058.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the copending application and the instant claims are drawn to a pharmaceutical composition comprise amlodipine and atorvastatin.

Thus, the instant claims 1-3 and 118-147 are deemed to be anticipated by the claims 1-3 and 118-147 of copending Application No. 10/214,058.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-6, 57-59 and 63-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 84-86 and 118-192 of copending Application No. 10/637781.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to a pharmaceutical composition comprise the same combination of amlodipine and atorvastatin while the copending application is drawn to a pharmaceutical kit comprise amlodipine and atorvastatin in two separate dosage forms, and container and directions for the administration of the two dosage forms.

Since the employment of a pharmaceutical kit or the patient pack comprising the same combination pharmaceutical composition in two dosage forms and directions for administering the dosage forms are all deemed obvious since they are all within the knowledge and conventional skills of pharmacologist to conveniently assist the user and prescriber for easy dispensary of the medication. Moreover, the inclusion of a package inserts including "indication and use" of the pharmaceutical composition in a pharmaceutical kit is mandated by 21 CFR 201.57 according to *Remington: The Science and Practice of Pharmacy*. Furthermore, with respect to the instructions or directions that direct one on how to use in a kit, the U.S. Court of Appeals for the Federal Circuit, *In re Ngai* 03-1524, recently rules that a kit of the prior art with a set of instructions is unpatentable (see the precedential opinion issued May 13, 2004).

Thus, the instant claims -6, 57-59 and 63-67 are deemed to be obvious over the claims 84-86 and 118-192 of copending Application No. 10/637781.

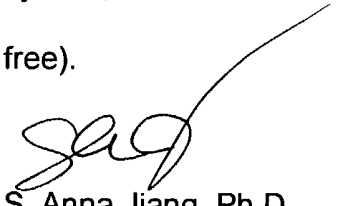
This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



S. Anna Jiang, Ph.D.
Primary Examiner, AU 1617
October 19, 2004